



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Lynch *et al.*

Appl. No. 09/961,381

Filed: September 25, 2001

For: **Model for Neurodegenerative  
Diseases Involving Amyloid  
Accumulation**

Confirmation No. 7154

Art Unit: 1632

Examiner: Crouch, D.

Atty. Docket: 1819.0040001/MAC/LBB

**First Supplemental Information Disclosure Statement**

Commissioner for Patents  
PO Box 1450  
Alexandria, VA 22313-1450  
Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this First Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Information Disclosure Statement filed electronically herewith, in connection with the above-captioned application. A copy of each document is also provided.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.

This First Supplemental Information Disclosure Statement is being filed more than three months after the U.S. filing date and after the mailing date of the first Office Action on the merits, but before the mailing date of a Final Rejection, or Notice of Allowance, or an action that otherwise closes prosecution in the application.

This IDS is being filed as two submissions on the same day. One submission is electronic and one submission is non-electronic. It is believed that only one fee under 37 C.F.R. §1.17(p) is required to cover both submissions. That fee is included with this non-electronic submission. Attached is our PTO-2038 Credit Card Payment Form in the amount of \$180.00 in payment of the fee under 37 C.F.R. § 1.17(p).

It is respectfully requested that the Examiner initial and return a copy of the enclosed PTO-1449, and indicate in the official file wrapper of this patent application that the documents have been considered.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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Attorney for Applicants  
Registration No. 35,086

Date: April 16, 2004  
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| <b>FIRST SUPPLEMENTAL<br/>INFORMATION DISCLOSURE STATEMENT</b><br><small>FORM PTO-1449</small> |  | ATTY. DOCKET NO.<br>1819.0040001/MAC/LBB | APPLICATION NO.<br>09/961,381 |
|  |  | APPLICANT<br>Lynch et al.                |                               |
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|------------------|-----|-----------------|------------|---------|-------|-----------|-------------|
|                  | AL1 | WO 92/00091 A1  | 01/09/1992 | WIPO    |       |           | Yes<br>No   |
|                  | AM1 | WO 93/20242 A1  | 10/14/1993 | WIPO    |       |           | Yes<br>No   |
|                  | AN  |                 |            |         |       |           | Yes<br>No   |
|                  | AO  |                 |            |         |       |           | Yes<br>No   |
|                  | AP  |                 |            |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|    |   |   |
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| AR | 1 | Akiyama, H., et al., "Inflammation and Alzheimer's disease," <i>Neurobiol. Aging</i> 21:383-421, Elsevier Science (May-June 2000)   |
| AS | 1 | Backstrom, J.R., et al., "Matrix Metalloproteinase-9 (MMP-9) Is Synthesized in Neurons of the Human Hippocampus and Is Capable of Degrading the Amyloid- $\beta$ Peptide (1-40)," <i>J. Neurosci.</i> 16:7910-7919, Society for Neuroscience (1996) |
| AT | 1 | Bahr, B.A., et al., "Stable Maintenance of Glutamate Receptors and Other Synaptic Components in Long-Term Hippocampal Slices," <i>Hippocampus</i> 5:425-439, Wiley-Liss (1995)  |

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|                     | AN |                 |      |         |       |           | Yes<br>No   |
|                     | AO |                 |      |         |       |           | Yes<br>No   |
|                     | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|    |   |  |
|----|---|--|
| AR | 2 | Bahr, B.A., et al., "Amyloid $\beta$ Protein is Internalized Selectively by Hippocampal Field CA1 and Causes Neurons to Accumulate Amyloidogenic Carboxyterminal Fragments of the Amyloid Precursor Protein," <i>J. Comp. Neurol.</i> 397:139-147, Wiley-Liss (1998) |
| AS | 2 | Bahr, B., and Lynch, G., "Purification of an Arg-Gly-Asp selective matrix receptor from brain synaptic plasma membranes," <i>Biochem. J.</i> 281:137-142, The Biochemical Society/Portland Press (1992)  |
| AT | 2 | Bahr, B.A., et al., "Fibronectin binding by brain synaptosomal membranes may not involve conventional integrins," <i>Neuroreport</i> 2:13-16, Rapid Communications of Oxford (1991)  |

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|                  | AO |                 |      |         |       |           | Yes<br>No   |
|                  | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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|----|---|--|
| AR | 3 | Bahr, B.A., et al., "Arg-Gly-Asp-Ser-Selective Adhesion and the Stabilization of Long-Term Potentiation: Pharmacological Studies and the Characterization of a Candidate Matrix Receptor," <i>J. Neurosci.</i> 17:1320-1329, Society for Neuroscience (1997) |
| AS | 3 | Bahr, B.A., "Integrin-Type Signaling Has a Distinct Influence on NMDA-Induced Cytoskeletal Disassembly," <i>J. Neurosci. Res.</i> 59:827-832, Wiley-Liss (March 2000)  |
| AT | 3 | Bard, F., et al., "Peripherally administered antibodies against amyloid $\beta$ -peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease," <i>Nat. Med.</i> 6:916-919, Nature America Inc. (August 2000)         |

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|----|---|--|
| AR | 4 | Barrett, A.J., and Kirschke, H., "Cathepsin B, Cathepsin H, and Cathepsin L," <i>Meth. Enzymol.</i> 80:535-561, Academic Press (1981)  |
| AS | 4 | Beattie, E.C., et al., "Regulation of AMPA receptor endocytosis by a signaling mechanism shared with LTD," <i>Nat. Neurosci.</i> 3:1291-1300, Nature America Inc. (December 2000)                                |
| AT | 4 | Bednarski, E., and Lynch, G., "Cytosolic Proteolysis of $\tau$ by Cathepsin D in Hippocampus Following Suppression of Cathepsins B and L," <i>J. Neurochem.</i> 67:1846-1855, Lippincott-Raven Publishers (1996) |

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**OTHER (Including Author, Title, Date, Pertinent Pages, etc.)**

|    |   |   |
|----|---|---|
| AR | 5 | Bednarski, E., and Lynch, G., "Selective suppression of cathepsin L results from elevations in lysosomal pH and is followed by proteolysis of tau protein," <i>NeuroReport</i> 9:2089-2094, <i>Rapid Science</i> (1998) |
| AS | 5 | Bi, X., et al., "Polarized Distribution of $\alpha$ 5 Integrin in Dendrites of Hippocampal and Cortical Neurons," <i>J. Comp. Neurol.</i> 435:184-193, Wiley-Liss (June 2001)   |
| AT | 5 | Bi, X., et al., "Novel Cathepsin D Inhibitors Block the Formation of Hyperphosphorylated Tau Fragments in Hippocampus," <i>J. Neurochem.</i> 74:1469-1477, Lippincott Williams & Wilkins (April 2000)                   |

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|    |   |   |
|----|---|---|
| AR | 6 | Brion, J.-P., et al., "Neurofilament Monoclonal Antibodies RT97 and 8D8 Recognize Different Modified Epitopes in Paired Helical Filament- $\tau$ in Alzheimer's Disease," <i>J. Neurochem.</i> 60:1372-1382, Raven Press (1993)               |
| AS | 6 | Bruce, A.J., et al., " $\beta$ -Amyloid toxicity in organotypic hippocampal cultures: Protection by EUK-8, a synthetic catalytic free radical scavenger," <i>Proc. Natl. Acad. Sci. USA</i> 93:2312-2316, National Academy of Sciences (1996) |
| AT | 6 | Burkin, D.J., et al., "A Functional Role for Specific Spliced Variants of the $\alpha 7\beta 1$ Integrin in Acetylcholine Receptor Clustering," <i>J. Cell Biol.</i> 143:1067-1075, The Rockefeller University Press (1998)                   |

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|----|---|--|
| AR | 7 | Burnashev, N., et al., "Control of Asparagine Residues of Calcium Permeability and Magnesium Blockade in the NMDA Receptor," <i>Science</i> 257:1415-1419, American Association for the Advancement of Science (1992)  |
| AS | 7 | Busciglio, J., et al., "Generation of $\beta$ -amyloid in the secretory pathway in neuronal and nonneuronal cells," <i>Proc. Natl. Acad. Sci. USA</i> 90:2092-2096, National Academy of Sciences (1993)  |
| AT | 7 | Callahan, L.M., et al., "Quantitative Decrease in Synaptophysin Message Expression and Increase in Cathepsin D Message Expression in Alzheimer Disease Neurons Containing Neurofibrillary Tangles," <i>J. Neuropathol. Exp. Neurol.</i> 58:275-287, American Association of Neuropathologists (March 1999) |

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| AL               |  |                 |      |         |       |           | Yes<br>No   |
| AM               |  |                 |      |         |       |           | Yes<br>No   |
| AN               |  |                 |      |         |       |           | Yes<br>No   |
| AO               |  |                 |      |         |       |           | Yes<br>No   |
| AP               |  |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|    |   |   |
|----|---|---|
| AR | 8 | Carroll, R.C., et al., "Dynamin-dependent endocytosis of ionotropic glutamate receptors," Proc. Natl. Acad. Sci. USA 96:14112-14117, National Academy of Sciences (November 1999)   |
| AS | 8 | Caswell, M.D., et al., "The amyloid $\beta$ -protein precursor of Alzheimer's disease is degraded extracellularly by a Kunitz protease inhibitor domain-sensitive trypsin-like serine protease in cultures of chick sympathetic neurons," Eur. J. Biochem. 266:509-516, Blackwell Science (December 1999) |
| AT | 8 | Cataldo, A.M., et al., "Gene Expression and Cellular Content of Cathepsin D in Alzheimer's Disease Brain: Evidence for Early Up-Regulation of the Endosomal-Lysosomal System," Neuron 14:671-680, Cell Press (1995)   |

| EXAMINER | DATE CONSIDERED |
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| FORM PTO-1449<br><b>FIRST SUPPLEMENTAL<br/>INFORMATION DISCLOSURE STATEMENT</b> |  | ATTY. DOCKET NO.<br>1819.0040001/MAC/LBB | APPLICATION NO.<br>09/961,381 |
|   |  | APPLICANT<br>Lynch et al.                |                               |
|   |  | FILING DATE<br>September 25, 2001        | GROUP<br>1632                 |

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| EXAMINER<br>INITIAL |    | DOCUMENT NUMBER | DATE | NAME | CLASS | SUB-CLASS | FILING DATE |
|---------------------|----|-----------------|------|------|-------|-----------|-------------|
|                     | AA |                 |      |      |       |           |             |
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## FOREIGN PATENT DOCUMENTS

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|---------------------|----|-----------------|------|---------|-------|-----------|-------------|
|                     | AL |                 |      |         |       |           | Yes<br>No   |
|                     | AM |                 |      |         |       |           | Yes<br>No   |
|                     | AN |                 |      |         |       |           | Yes<br>No   |
|                     | AO |                 |      |         |       |           | Yes<br>No   |
|                     | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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|----|---|--|
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| AS | 9 | Chazot, P.L., "CP-101606," <i>Curr. Opin. Investig. Drugs</i> 1:370-374, PharmaPress (November 2000)   |
| AT | 9 | Chen, C., et al., "'Analogous' Organic Synthesis of Small-Compound Libraries: Validation of Combinatorial Chemistry in Small-Molecule Synthesis," <i>J. Am. Chem. Soc.</i> 116:2661-2662, American Chemical Society (1994) |

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|   |  | APPLICANT<br>Lynch et al.                |                               |
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|                  | AN |                 |      |         |       |           | Yes<br>No   |
|                  | AO |                 |      |         |       |           | Yes<br>No   |
|                  | AP |                 |      |         |       |           | Yes<br>No   |

**OTHER (Including Author, Title, Date, Pertinent Pages, etc.)**

|  |    |           |   |
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|  | AR | <u>10</u> | Chun, D., et al., "Evidence that Integrins Contribute to Multiple Stages in the Consolidation of Long Term Potentiation in Rat Hippocampus," <i>Neurosci.</i> 105:815-829, Elsevier Science (August 2001) |
|  | AS | <u>10</u> | Cotran, R.S., et al., "Forebrain Anomalies," in <i>Robbins Pathologic Basis of Disease</i> , 6 <sup>th</sup> ed., Schmitt, B., ed., W.B. Saunders Co., Philadelphia, PA, p. 1300-1301 (1998)              |
|  | AT | <u>10</u> | Cotran, R.S., et al., "Neurofibrillary tangles," in <i>Robbins Pathologic Basis of Disease</i> , 6 <sup>th</sup> ed., Schmitt, B., ed., W.B. Saunders Co., Philadelphia, PA, p.1330 (1998)                |

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|   |  | APPLICANT<br>Lynch et al.                |  | FILING DATE<br>September 25, 2001 |  |

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|                     | AN |                 |      |         |       |           | Yes<br>No   |
|                     | AO |                 |      |         |       |           | Yes<br>No   |
|                     | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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|----|-----------|--|
| AR | <u>11</u> | Cras, P., et al., "Microglia are associated with the extracellular neurofibrillary tangles of Alzheimer disease," <i>Brain Res.</i> 558:312-314, Elsevier Science B.V. (1991)                                  |
| AS | <u>11</u> | Dunah, A.W., et al., " $\alpha$ -Actinin-2 in rat striatum: localization and interaction with NMDA glutamate receptor subunits," <i>Brain Res. Mol. Brain Res.</i> 79:77-87, Elsevier Science B.V. (June 2000) |
| AT | <u>11</u> | Ehlers, M.D., "Reinsertion or Degradation of AMPA Receptors Determined Activity-Dependent Endocytic Sorting," <i>Neuron</i> 28:511-525, Cell Press (November 2000)   |

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|   |  | FILING DATE<br>September 25, 2001        |  | GROUP<br>1632                 |  |

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|                  | AL |                 |      |         |       |           | Yes<br>No   |
|                  | AM |                 |      |         |       |           | Yes<br>No   |
|                  | AN |                 |      |         |       |           | Yes<br>No   |
|                  | AO |                 |      |         |       |           | Yes<br>No   |
|                  | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|  |    |           |  |
|--|----|-----------|--|
|  | AR | <u>12</u> | Fox, N., et al., "Seeing what Alzheimer saw-with magnetic resonance microscopy," Nat. Med. 6:20-21, Nature America (January 2000)  |
|  | AS | <u>12</u> | Frenkel, D., et al., "Immunization against Alzheimer's $\beta$ -amyloid plaques via EFRH phage administration," Proc. Natl. Acad. Sci. USA 97:11455-11459, National Academy of Sciences (October 2000) |
|  | AT | <u>12</u> | Games, D., et al., "Lack of Alzheimer Pathology After $\beta$ -Amyloid Protein Injections in Rat Brain," Neurobiol. Aging 13:569-576, Pergamon Press (1992)  |

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| FORM PTO-1449  |  |  | ATTY. DOCKET NO.<br>1819.0040001/MAC/LBB | APPLICATION NO.<br>09/961,381 |
| <u>FIRST SUPPLEMENTAL</u><br><u>INFORMATION DISCLOSURE STATEMENT</u> |  |  | APPLICANT<br>Lynch et al.                |                               |
|  |  |  | FILING DATE<br>September 25, 2001        | GROUP<br>1632                 |

## U.S. PATENT DOCUMENTS

| EXAMINER INITIAL |    | DOCUMENT NUMBER | DATE | NAME | CLASS | SUB-CLASS | FILING DATE |
|------------------|----|-----------------|------|------|-------|-----------|-------------|
|                  | AA |                 |      |      |       |           |             |
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|                  | AC |                 |      |      |       |           |             |
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## FOREIGN PATENT DOCUMENTS

| EXAMINER INITIAL |    | DOCUMENT NUMBER | DATE | COUNTRY | CLASS | SUB-CLASS | TRANSLATION |
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|                  | AL |                 |      |         |       |           | Yes<br>No   |
|                  | AM |                 |      |         |       |           | Yes<br>No   |
|                  | AN |                 |      |         |       |           | Yes<br>No   |
|                  | AO |                 |      |         |       |           | Yes<br>No   |
|                  | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|    |           |  |
|----|-----------|--|
| AR | <u>13</u> | Ghiso, J., et al., "A 109-amino-acid C-terminal fragment of Alzheimer's-disease amyloid precursor protein contains a sequence, -RHDS-, that promotes cell adhesion," <i>Biochem. J.</i> 288:1053-1059, Portland Press (1992) |
| AS | <u>13</u> | Ginsberg, S.D., et al., "Expression Profile of Transcripts in Alzheimer's Disease Tangle-Bearing CA1 Neurons," <i>Ann. Neurol.</i> 48:77-87, Lippincott Williams & Wilkins (July 2000)                                       |
| AT | <u>13</u> | Gordon, I., et al., "Memory deficits and cholinergic impairments in apolipoprotein E-deficient mice," <i>Neurosci. Lett.</i> 199:1-4, Elsevier Science Ireland (1995)  |

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|   |  | APPLICANT<br>Lynch et al.                |                               |
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| AL               |  |                 |      |         |       |           | Yes<br>No   |
| AM               |  |                 |      |         |       |           | Yes<br>No   |
| AN               |  |                 |      |         |       |           | Yes<br>No   |
| AO               |  |                 |      |         |       |           | Yes<br>No   |
| AP               |  |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|    |           |   |
|----|-----------|---|
| AR | <u>14</u> | Gottlieb, T.A., et al., "Actin Microfilaments Play a Critical Role in Endocytosis at the Apical but not the Basolateral Surface of Polarized Epithelial Cells," <i>J. Cell Biol.</i> 120:695-710, The Rockefeller University Press (1993) |
| AS | <u>14</u> | Gouras, G.K., et al., "Intraneuronal A $\beta$ 42 Accumulation in Human Brain," <i>Am. J. Pathol.</i> 156:15-20, American Society for Investigative Pathology (January 2000)  |
| AT | <u>14</u> | Guénette, S.Y., and Tanzi, R.E., "Progress toward valid transgenic mouse models for Alzheimer's disease," <i>Neurobiol. Aging</i> 20:201-211, Elsevier Science (March-April 1999)   |

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|                  | AM |                 |      |         |       |           | Yes<br>No   |
|                  | AN |                 |      |         |       |           | Yes<br>No   |
|                  | AO |                 |      |         |       |           | Yes<br>No   |
|                  | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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|----|-----------|--|
| AR | <u>15</u> | Haass, C., et al., "Mutations Associated with a Locus for Familial Alzheimer's Disease Result in Alternative Processing of Amyloid $\beta$ -Protein Precursor," <i>J. Biol. Chem.</i> 269:17741-17748, The American Society for Biochemistry and Molecular Biology (1994)        |
| AS | <u>15</u> | Haass, C., et al., "Targeting of cell-surface $\beta$ -amyloid precursor protein to lysosomes: alternative processing into amyloid-bearing fragments," <i>Nature</i> 357:500-503, Macmillan Magazines (1992)   |
| AT | <u>15</u> | Harper, J.D., and Lansbury, Jr., P.T., "Models of Amyloid Seeding in Alzheimer's Disease and Scrapie: Mechanistic Truths and Physiological Consequences of the Time-Dependent Solubility of Amyloid Proteins," <i>Annu. Rev. Biochem.</i> 66:385-407, Annual Reviews Inc. (1997) |

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|          |           |  |
|----------|-----------|--|
| AR       | <u>16</u> | Harris-White, M.E., et al., "Effects of Transforming Growth Factor- $\beta$ (Isoforms 1-3) on Amyloid- $\beta$ Deposition, Inflammation, and Cell Targeting in Organotypic Hippocampal Slice Cultures," <i>J. Neurosci</i> 18:10366-10374, Society for Neuroscience (1998) |
| AS       | <u>16</u> | Hoffman, K.B., et al., " $\beta$ -Amyloid increases cathepsin D levels in hippocampus," <i>Neurosci. Lett.</i> 250:75-78, Elsevier Science Ireland (1998)  |
| AT       | <u>16</u> | Hsia, A.Y., et al., "Plaque-independent disruption of neural circuits in Alzheimer's disease mouse models," <i>Proc. Natl. Acad. Sci. USA</i> 96:3228-3233, National Academy of Sciences (March 1999)  |
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|   |  |  | APPLICANT<br>Lynch et al.                |                               |
|   |  |  | FILING DATE<br>September 25, 2001        | GROUP<br>1632                 |

## U.S. PATENT DOCUMENTS

| EXAMINER<br>INITIAL |    | DOCUMENT NUMBER | DATE | NAME | CLASS | SUB-CLASS | FILING DATE |
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|                     | AA |                 |      |      |       |           |             |
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## FOREIGN PATENT DOCUMENTS

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|---------------------|----|-----------------|------|---------|-------|-----------|-------------|
|                     | AL |                 |      |         |       |           | Yes<br>No   |
|                     | AM |                 |      |         |       |           | Yes<br>No   |
|                     | AN |                 |      |         |       |           | Yes<br>No   |
|                     | AO |                 |      |         |       |           | Yes<br>No   |
|                     | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|  |    |           |  |
|--|----|-----------|--|
|  | AR | <u>17</u> | Huang, T.-F., "What have snakes taught us about integrins," <i>Cell. Mol. Life Sci.</i> 54:527-540, Birkhäuser Verlag (1998)   |
|  | AS | <u>17</u> | Huse, W.D., et al., "Generation of a Large Combinatorial Library of the Immunoglobulin Repertoire in Phage Lambda," <i>Science</i> 246:1275-1281, American Association for the Advancement of Science (1989) |
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|                  | AL |                 |      |         |       |           | Yes<br>No   |
|                  | AM |                 |      |         |       |           | Yes<br>No   |
|                  | AN |                 |      |         |       |           | Yes<br>No   |
|                  | AO |                 |      |         |       |           | Yes<br>No   |
|                  | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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|----|-----------|--|
| AR | <u>18</u> | Iwata, N., et al., "Identification of the major A $\beta$ <sub>1-42</sub> -degrading catabolic pathway in brain parenchyma: Suppression leads to biochemical and pathological deposition," <i>Nat. Med.</i> 6:143-150, Nature America Inc. (February 2000) |
| AS | <u>18</u> | Janus, C., et al., "Transgenic mouse models of Alzheimer's disease," <i>Biochim. Biophys. Acta</i> 1502:63-75, Elsevier Science B.V. (July 2000)   |
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|                  | AN |                 |      |         |       |           | Yes<br>No   |
|                  | AO |                 |      |         |       |           | Yes<br>No   |
|                  | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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|  | AS | <u>19</u> | Köhler, G., and Milstein, C., "Continuous cultures of fused cells secreting antibody of predefined specificity," <i>Nature</i> 256:495-497, Macmillan Journals (1975)   |
|  | AT | <u>19</u> | Kuo, Y.-M., et al., "Water-soluble A $\beta$ (N-40, N-42) Oligomers in Normal and Alzheimer Disease Brains," <i>J. Biol. Chem.</i> 271:4077-4081, The American Society for Biochemistry and Molecular Biology (1996)  |

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|                  | AN |                 |      |         |       |           | Yes<br>No   |
|                  | AO |                 |      |         |       |           | Yes<br>No   |
|                  | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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|--|----|-----------|--|
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|  | AS | <u>20</u> | Le Varlet, B., et al., "Age-Related Functional and Structural Changes in Human Dermo-Epidermal Junction Components," <i>J. Investig. Dermatol. Symp. Proc.</i> 3:172-179, The Society for Investigative Dermatology, Inc. (1998) |
|  | AT | <u>20</u> | Marsh, M., and McMahon, H.T., "The Structural Era of Endocytosis," <i>Science</i> 285:215-220, American Association for the Advancement of Science (July 1999)   |

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|   |  |  | APPLICANT<br>Lynch et al.                |                               |
|   |  |  | FILING DATE<br>September 25, 2001        | GROUP<br>1632                 |

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|                  | AL |                 |      |         |       |           | Yes<br>No   |
|                  | AM |                 |      |         |       |           | Yes<br>No   |
|                  | AN |                 |      |         |       |           | Yes<br>No   |
|                  | AO |                 |      |         |       |           | Yes<br>No   |
|                  | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|    |           |  |
|----|-----------|--|
| AR | <u>21</u> | Matter, M.L., et al., "The $\alpha 5\beta 1$ Integrin Mediates Elimination of Amyloid- $\beta$ Peptide and Protects Against Apoptosis," <i>J. Cell. Biol.</i> 141:1019-1030, The Rockefeller University Press (1998) |
| AS | <u>21</u> | Miller, D.L., et al., "Peptide Compositions of the Cerebrovascular and Senile Plaque Core Amyloid Deposits of Alzheimer's Disease," <i>Arch. Biochem. Biophys.</i> 301:41-52, Academic Press (1993)                  |
| AT | <u>21</u> | Morgan, D., et al., "A $\beta$ peptide vaccination prevents memory loss in an animal model of Alzheimer's disease," <i>Nature</i> 408:982-985, Nature Publishing Group (December 2000)                               |

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|   |  | APPLICANT<br>Lynch et al.                |  | FILING DATE<br>September 25, 2001 |  |

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| AL               |  |                 |      |         |       |           | Yes<br>No   |
| AM               |  |                 |      |         |       |           | Yes<br>No   |
| AN               |  |                 |      |         |       |           | Yes<br>No   |
| AO               |  |                 |      |         |       |           | Yes<br>No   |
| AP               |  |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|    |           |   |
|----|-----------|---|
| AR | <u>22</u> | Morris, J.C., "The Clinical Dementia Rating (CDR): Current version and scoring rules," <i>Neurology</i> 43:2412-2414, Advanstar Communications (1993)   |
| AS | <u>22</u> | Mucke, L., et al., "High-Level Neuronal Expression of A $\beta$ <sub>1-42</sub> in Wild-Type Human Amyloid Protein Precursor Transgenic Mice: Synaptotoxicity without Plaque Formation," <i>J. Neurosci.</i> 20:4050-4058, Society for Neuroscience (June 2000) |
| AT | <u>22</u> | Mueller, A.L., et al., "NPS 1506, A Novel NMDA Receptor Antagonist and Neuroprotectant," <i>Ann. N.Y. Acad. Sci.</i> 890:450-457, New York Academy of Sciences (December 1999)  |

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| AO               |  |                 |      |         |       |           | Yes<br>No   |
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## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|    |           |  |
|----|-----------|--|
| AR | <u>23</u> | Muller, D., et al., "Time course of synaptic development in hippocampal organotypic cultures," <i>Dev. Brain Res.</i> 71:93-100, Elsevier Science B.V. (1993)  |
| AS | <u>23</u> | Murphy, Jr., G.M., et al., "Expression of Macrophage Colony-Stimulating Factor receptor Is Increased in the A $\beta$ PP <sup>V717F</sup> Transgenic Mouse Model of Alzheimer's Disease," <i>Am. J. Pathol.</i> 157:895-904, American Society for Investigative Pathology (September 2000) |
| AT | <u>23</u> | Nakanishi, H., et al., "Age-Related Changes in Activities and Localizations of Cathepsins D, E, B, and L in the Rat Brain Tissues," <i>Exp. Neurol.</i> 126:119-128, Academic Press (1994)   |

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|  |    |           |   |
|--|----|-----------|---|
|  | AR | <u>24</u> | Nathan, B.P., et al., "Apolipoprotein E3- and E4-Induced Differences in Neurite Outgrowth Are Associated with Differences in the Subcellular Localization of Apolipoprotein E," <i>Soc. Neurosci. 20</i> (Part 2):1033, Abs. No. 421.5, Society for Neuroscience (1994) |
|  | AS | <u>24</u> | NCBI Entrez, Genbank Report, Accession No. D00466, Rajavashisth, T.B., et al. (1993)  |
|  | AT | <u>24</u> | NCBI Entrez, Genbank Report, Accession No. M10065, Das, H.K., et al. (1993)   |

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|                  | AL |                 |      |         |       |           | Yes<br>No   |
|                  | AM |                 |      |         |       |           | Yes<br>No   |
|                  | AN |                 |      |         |       |           | Yes<br>No   |
|                  | AO |                 |      |         |       |           | Yes<br>No   |
|                  | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|    |           |   |
|----|-----------|---|
| AR | <u>25</u> | Nemerow, G.R., and Stewart, P.L., "Role of $\alpha_v$ Integrins in Adenovirus Cell Entry and Gene Delivery," <i>Microbiol. Mol. Biol. Rev.</i> 63:725-734, American Society for Microbiology (September 1999) |
| AS | <u>25</u> | Palmer, G.C., "Neuroprotection by NMDA Receptor Antagonists in a Variety of Neuropathologies," <i>Curr. Drug Targets</i> 2:241-271, Bentham Science Publishers (September 2001)                               |
| AT | <u>25</u> | Perlmutter, L.S., et al., "Morphological association between microglia and senile plaque amyloid in Alzheimer's disease," <i>Neurosci. Lett.</i> 119:32-36, Elsevier Scientific Publishers Ireland (1990)     |

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| FORM PTO-1449<br><b>FIRST SUPPLEMENTAL<br/>INFORMATION DISCLOSURE STATEMENT</b> |  | ATTY. DOCKET NO.<br>1819.0040001/MAC/LBB | APPLICATION NO.<br>09/961,381 |
|   |  | APPLICANT<br>Lynch et al.                |                               |
|   |  | FILING DATE<br>September 25, 2001        | GROUP<br>1632                 |

## U.S. PATENT DOCUMENTS

| EXAMINER INITIAL |    | DOCUMENT NUMBER | DATE | NAME | CLASS | SUB-CLASS | FILING DATE |
|------------------|----|-----------------|------|------|-------|-----------|-------------|
|                  | AA |                 |      |      |       |           |             |
|                  | AB |                 |      |      |       |           |             |
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## FOREIGN PATENT DOCUMENTS

| EXAMINER INITIAL |    | DOCUMENT NUMBER | DATE | COUNTRY | CLASS | SUB-CLASS | TRANSLATION |
|------------------|----|-----------------|------|---------|-------|-----------|-------------|
|                  | AL |                 |      |         |       |           | Yes<br>No   |
|                  | AM |                 |      |         |       |           | Yes<br>No   |
|                  | AN |                 |      |         |       |           | Yes<br>No   |
|                  | AO |                 |      |         |       |           | Yes<br>No   |
|                  | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|    |           |   |
|----|-----------|---|
| AR | <u>26</u> | Peterson, R.C., et al., "Apolipoprotein E Status as a Predictor of the Development of Alzheimer's Disease in Memory-Impaired Individuals," <i>J. Am. Med. Assoc.</i> 273:1274-1278, American Medical Association (1995) |
| AS | <u>26</u> | Pierschbacher, M.D., and Ruoslahti, E., "Cell attachment activity of fibronectin can be duplicated by small synthetic fragments of the molecule," <i>Nature</i> 309:30-33, Macmillan Journals (1984)                    |
| AT | <u>26</u> | Pinkstaff, J.K., et al., "Integrin Subunit Gene Expression Is Regionally Differentiated in Adult Brain," <i>J. Neurosci.</i> 19:1541-1556, Society for Neuroscience (March 1999)  |

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|  |  | APPLICANT<br>Lynch et al.                |                               |
|  |  | FILING DATE<br>September 25, 2001        | GROUP<br>1632                 |

| U.S. PATENT DOCUMENTS |    |                 |      |      |       |           |             |
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|                          | AL |                 |      |         |       |           | Yes<br>No   |
|                          | AM |                 |      |         |       |           | Yes<br>No   |
|                          | AN |                 |      |         |       |           | Yes<br>No   |
|                          | AO |                 |      |         |       |           | Yes<br>No   |
|                          | AP |                 |      |         |       |           | Yes<br>No   |

| OTHER (Including Author, Title, Date, Pertinent Pages, etc.) |    |    |   |  |  |  |  |
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|   |  | APPLICANT<br>Lynch et al.                |  |                               |  |
|   |  | FILING DATE<br>September 25, 2001        |  | GROUP<br>1632                 |  |

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|                  | AL |                 |      |         |       |           | Yes<br>No   |
|                  | AM |                 |      |         |       |           | Yes<br>No   |
|                  | AN |                 |      |         |       |           | Yes<br>No   |
|                  | AO |                 |      |         |       |           | Yes<br>No   |
|                  | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

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|--|----|-----------|--|
|  | AR | <u>28</u> | Proescholdt, M., et al., "Neuroprotection of S(+) ketamine isomer in global forebrain ischemia," <i>Brain Res.</i> 904:245-251, Elsevier Science B.V. (June 2001)  |
|  | AS | <u>28</u> | Qiu, W.Q., et al., "Insulin-degrading Enzyme Regulates Extracellular Levels of Amyloid $\beta$ -Protein by Degradation," <i>J. Biol. Chem.</i> 273:32730-32738, The American Society for Biochemistry and Molecular Biology (1998) |
|  | AT | <u>28</u> | Rao, V.L.R., et al., "Neuroprotection by memantine, a non-competitive NMDA receptor antagonist after traumatic brain injury in rats," <i>Brain Res.</i> 911:96-100, Elsevier Science B.V. (August 2001)                            |

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|   |  | FILING DATE<br>September 25, 2001        | GROUP<br>1632                 |

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| AL               |  |                 |      |         |       |           | Yes<br>No   |
| AM               |  |                 |      |         |       |           | Yes<br>No   |
| AN               |  |                 |      |         |       |           | Yes<br>No   |
| AO               |  |                 |      |         |       |           | Yes<br>No   |
| AP               |  |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|    |           |   |
|----|-----------|---|
| AR | <u>29</u> | Ruoslahti, E., "RGD and Other Recognition Sequences for Integrins," <i>Annu. Rev. Cell Dev. Biol.</i> 12:697-715, Annual Reviews Inc. (1996)  |
| AS | <u>29</u> | Sabo, S., et al., "Interaction of beta-amyloid peptides with integrins in a human nerve cell line," <i>Neurosci. Lett.</i> 184:25-28, Elsevier Science Ireland (1995)               |
| AT | <u>29</u> | Schenk, D., et al., "Immunization with amyloid- $\beta$ attenuates Alzheimer-disease-like pathology in the PDAPP mouse," <i>Nature</i> 400:173-177, Macmillan Magazines (July 1999) |

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|   |  | APPLICANT<br>Lynch et al.                |                               |
|   |  | FILING DATE<br>September 25, 2001        | GROUP<br>1632                 |

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| EXAMINER<br>INITIAL |  | DOCUMENT NUMBER | DATE | NAME | CLASS | SUB-CLASS | FILING DATE |
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| AH                  |  |                 |      |      |       |           |             |
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|---------------------|--|-----------------|------|---------|-------|-----------|-------------|
| AL                  |  |                 |      |         |       |           | Yes<br>No   |
| AM                  |  |                 |      |         |       |           | Yes<br>No   |
| AN                  |  |                 |      |         |       |           | Yes<br>No   |
| AO                  |  |                 |      |         |       |           | Yes<br>No   |
| AP                  |  |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|    |           |   |
|----|-----------|---|
| AR | <u>30</u> | Scheuner, D., et al., "Secreted amyloid $\beta$ -protein similar to that in the senile plaques of Alzheimer's disease is increased <i>in vivo</i> by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease," <i>Nat. Med.</i> 2:864-870, Nature Publishing Co. (1996) |
| AS | <u>30</u> | Seiler, C., and Nicolson, T., "Defective Calmodulin-Dependent Rapid Apical Endocytosis in Zebrafish Sensory Hair Cell Mutants," <i>J. Neurobiol.</i> 41:424-434, John Wiley & Sons (November 1999)  |
| AT | <u>30</u> | Selkoe, D.J., "Cell Biology of the Amyloid $\beta$ -Protein Precursor and the Mechanism of Alzheimer's Disease," <i>Annu. Rev. Cell. Biol.</i> 10:373-403, Annual Reviews Inc. (1994)   |

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|   |  |  | APPLICANT<br>Lynch et al.                |  |                               |  |  |
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|                     | AL |                 |      |         |       |           | Yes<br>No   |
|                     | AM |                 |      |         |       |           | Yes<br>No   |
|                     | AN |                 |      |         |       |           | Yes<br>No   |
|                     | AO |                 |      |         |       |           | Yes<br>No   |
|                     | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|  |    |           |  |
|--|----|-----------|--|
|  | AR | <u>31</u> | Selkoe, D.J., "Imaging Alzheimer's amyloid," <i>Nat. Biotechnol.</i> 18:823-824, Nature America (August 2000)  |
|  | AS | <u>31</u> | Shoji, M., et al., "Production of the Alzheimer Amyloid $\beta$ Protein by Normal Proteolytic Processing," <i>Science</i> 258:126-129, American Association for the Advancement of Science (1992)      |
|  | AT | <u>31</u> | Steiner, H., et al., "Genes and mechanisms involved in $\beta$ -amyloid generation and Alzheimer's disease," <i>Eur. Arch. Psychiatry Clin. Neurosci.</i> 249:266-270, Springer-Verlag (December 1999) |

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| AM               |  |                 |      |         |       |           | Yes<br>No   |
| AN               |  |                 |      |         |       |           | Yes<br>No   |
| AO               |  |                 |      |         |       |           | Yes<br>No   |
| AP               |  |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|    |           |  |
|----|-----------|--|
| AR | <u>32</u> | Stoppini, L., et al., "A simple method for organotypic cultures of nervous tissue," <i>J. Neurosci. Meth.</i> 37:173-182, Elsevier Science B.V. (1991)   |
| AS | <u>32</u> | Striessmatter, W.J., et al., "Hypothesis: Microtubule Instability and Paired Helical Filament Formation in the Alzheimer Disease Brain Are Related to Apolipoprotein E Genotype," <i>Exp. Neurol.</i> 125:163-171, Academic Press (1994) |
| AT | <u>32</u> | Sturchler-Pierrat, C., and Sommer, B., "Transgenic Animals in Alzheimer's Disease Research," <i>Rev. Neurosci.</i> 10:15-24, Freund & Pettman (January 1999)   |

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|                  | AN |                 |      |         |       |           | Yes<br>No   |
|                  | AO |                 |      |         |       |           | Yes<br>No   |
|                  | AP |                 |      |         |       |           | Yes<br>No   |

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|    |           |   |
|----|-----------|---|
| AR | <u>33</u> | Suzuki, N., et al., "An Increased Percentage of Long Amyloid $\beta$ Protein Secreted by Familial Amyloid $\beta$ Protein Precursor ( $\beta$ APP <sub>717</sub> ) Mutants," <i>Science</i> 264:1336-1340, American Association for the Advancement of Science (1994) |
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| AT | <u>33</u> | Tsao, P.W., and Mousa, S.A., "Thrombospondin Mediates Calcium Mobilization in Fibroblasts via Its Arg-Gly-Asp and Carboxyl-terminal Domains," <i>J. Biol. Chem.</i> 270:23747-23753, The American Society for Biochemistry and Molecular Biology (1995)               |

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| FORM PTO-1449<br><b>FIRST SUPPLEMENTAL<br/>INFORMATION DISCLOSURE STATEMENT</b> |  | ATTY. DOCKET NO.<br>1819.0040001/MAC/LBB |  | APPLICATION NO.<br>09/961,381 |  |
|   |  | APPLICANT<br>Lynch et al.                |  |                               |  |
|   |  | FILING DATE<br>September 25, 2001        |  | GROUP<br>1632                 |  |

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|                  | AA |                 |      |      |       |           |             |
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|------------------|----|-----------------|------|---------|-------|-----------|-------------|
|                  | AL |                 |      |         |       |           | Yes<br>No   |
|                  | AM |                 |      |         |       |           | Yes<br>No   |
|                  | AN |                 |      |         |       |           | Yes<br>No   |
|                  | AO |                 |      |         |       |           | Yes<br>No   |
|                  | AP |                 |      |         |       |           | Yes<br>No   |

## OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

|  |    |           |   |
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|  | AR | <u>34</u> | van Leuven, F., "Single and multiple transgenic mice as models for Alzheimer's disease," <i>Prog. Neurobiol.</i> 61:305-312, Elsevier Science (June 2000)   |
|  | AS | <u>34</u> | Vekrellis, K., et al., "Neurons Regulate Extracellular Levels of Amyloid $\beta$ -Protein via Proteolysis by Insulin-Degrading Enzyme," <i>J. Neurosci.</i> 20:1657-1665, Society for Neuroscience (March 2000) |
|  | AT | <u>34</u> | Vigo-Pelfrey, C., et al., "Characterization of $\beta$ -Amyloid Peptide from Human Cerebrospinal Fluid," <i>J. Neurochem.</i> 61:1965-1968, Raven Press (1993)  |

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| AN               |  |                 |      |         |       |           | Yes<br>No   |
| AO               |  |                 |      |         |       |           | Yes<br>No   |
| AP               |  |                 |      |         |       |           | Yes<br>No   |

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|----|-----------|--|
| AR | <u>35</u> | Vincent, I., et al., "Mitotic Phosphoepitopes Precede Paired Helical Filaments in Alzheimer's Disease," <i>Neurobiol. Aging</i> 19:287-296, Elsevier Science (1998)  |
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| AT | <u>35</u> | Ward, E.S., et al., "Binding activities of a repertoire of single immunoglobulin variable domains secreted from <i>Escherichia coli</i> ," <i>Nature</i> 341:544-546, Macmillan Magazines (1989)                                   |

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|  | AR | <u>36</u> | Woods, A.G., et al., "Dexamethasone Selectively Suppresses Microglial Trophic Responses to Hippocampal Deafferentation," <i>Neurosci.</i> 91:1277-1289, Elsevier Science (July 1999)                                       |
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|  | AT | <u>36</u> | Yamazaki, T., et al., "Cell Surface Amyloid $\beta$ -Protein Precursor Colocalizes with $\beta_1$ Integrins at Substrate Contact Sites in Neural Cells," <i>J. Neurosci.</i> 17:1004-1010, Society for Neuroscience (1997) |

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|  | AS | <u>37</u> | International Search Report for International Patent Application No. PCT/US01/29788, mailed June 21, 2002.   |  |  |  |  |
|  | AT |           |  |  |  |  |  |

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